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New insights in diagnosis and treatment of differentiated thyroid carcinoma

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SUMMARY

The management of patients with differentiated thyroid cancer is the main topic of this thesis.

Chapter 1 gives a short introduction in the anatomy and physiology of the thyroid gland. Knowledge about the regulation of thyroid growth and the transformation into a malignant thyroid tumor is summarized. Thyroid tumors can be divided in several histologic types, of which differentiated thyroid carcinoma is the most common form. In most differentiated thyroid cancers three important functional features of the normal thyroid cell are preserved, namely, the ability to respond to thyroid stimulating hormone (TSH), the ability to accumulate iodide and the ability to secrete thyroglobulin. These specific functional features are utilized in the management of patients with differentiated thyroid carcinoma.

In **chapter 2** arguments for a genetic basis of differentiated thyroid carcinoma are described. The arguments can be found in epidemiological data, in the occurrence of occult carcinomas, in the occurrence of multifocality of the tumor and in the risk factors for tumor development. In approximately 5% of patients the differentiated thyroid cancer is dominantly inherited. Existing knowledge about germline mutations and somatic mutations in differentiated thyroid carcinoma is described. Currently, research into a specific germline mutation as basis for the development of familial differentiated thyroid carcinoma has yielded inconclusive results. Several genes have already been implicated, but no single locus has yet been identified by linkage analysis. It is hypothesized that association analysis will be of more value in elucidating the genetic base of differentiated thyroid cancer than linkage analysis.

Chapter 3 gives an overview of the management of differentiated thyroid carcinoma in elderly patients. Approximately 25% of the patients in which differentiated thyroid cancer is diagnosed, is 60 years or older. The prognosis of elderly patients is poor compared to younger patients, because old patients more often present with poor prognostic features, such as large tumors, follicular or Hürthle cell subtypes, extrathyroidal growth and distant metastases. Current therapy consists of a total thyroidectomy, if necessary combined with a lymph node dissection and followed by radioiodine ablation. Radioiodine therapy in elderly patients meets specific problems, concerning thyroid hormone withdrawal, side effects of ^{131}I and nursing problems. Special attention is given to the use of external radiotherapy, chemotherapy and hormonal therapy in elderly patients. Additional treatment of residual, recurrent or metastatic disease must be tailored, according to the stage of the disease, and should not be denied on the basis of chronological age. Lifelong treatment with suppressive thyroid hormone therapy does not lead to long-term side effects at old age.

Because of the rarity of differentiated thyroid carcinoma and the high overall survival rate, prospective randomized studies addressing issues of diagnosis, treatment and follow-up, are hardly available. It is unlikely that such studies will become available in the near future. Instead, data from large patient cohort studies has to learn the clinicians, what is the best way to treat patients with differentiated thyroid carcinoma. In **chapter 4** the results are presented of a cohort of 504 patients with differentiated thyroid carcinoma, referred to the Department of Endocrinology of the University Hospital Groningen for treatment with radioiodine over the past 23 years. All patients were initially treated with (near-) total thyroidectomy and 97% of patients received ^{131}I ablation for residual thyroid tissue. Efficacy of ablation was checked after 3 months. Residual disease was treated in a 3 months treatment interval with ^{131}I . A follow-up regimen, including annual physical examination and serum thyroglobulin measurements without diagnostic ^{131}I whole-body scintigraphy, was used for patients in complete remission. Mean follow-up was 9 years (range: 1 month - 23 years). In 85% of patients ablation, checked after 3 months, was successful and in 59% of patients treatment was completed within 6 months after initial surgery. At 10 year the overall survival was 87%. Recurrence occurred in 8.5% of patients. Risk factors for recurrence were older age at presentation, extrathyroidal growth and follicular or Hürthle cell subtype. It was concluded that the efficacy of ^{131}I ablation in patients with differentiated thyroid carcinoma can be successfully checked already after 3 months. The reported treatment strategy with a short ^{131}I treatment interval shows a low recurrence rate and a high overall survival rate. These results justify a follow-up regimen limited to annual physical examination and serum thyroglobulin measurements for patients in complete remission.

In the literature considerable variations exist in the follow-up protocols for patients with differentiated thyroid carcinoma after initial treatment with total thyroidectomy and radioiodine ablation. Most protocols rely on serial diagnostic ^{131}I imaging and serum thyroglobulin measurements. The applied diagnostic ^{131}I doses vary between 37 and 370 MBq. Better lesion detectability is obtained by higher diagnostic doses. The aim of the study, described in **chapter 5** was to determine the yield of a high-dose diagnostic scan with 370 MBq ^{131}I in patients with a negative low-dose diagnostic scan with 74 MBq ^{131}I . Retrospective evaluation was performed in 158 patients, who received a high-dose diagnostic scan with 370 MBq ^{131}I because of a negative low-dose diagnostic scan with 74 MBq ^{131}I . In 127 (80%) of patients the 370 MBq ^{131}I scan was negative, similar to the preceding low-dose scan. In 31 (20%) of patients abnormal uptake was present on the 370 MBq diagnostic scan. In 19 of these 31 patients serum thyroglobulin was undetectable. Special attention was paid to the patients with positive high-dose diagnostic scanning and undetectable serum thyroglobulin levels after thyroid hormone withdrawal. The high-dose diagnostic scan was false positive in seven patients and solitary thyroid bed uptake was seen in eight patients. In only four patients (2.5%) the high-dose diagnostic scans revealed relevant uptake caused by residual differentiated thyroid cancer. It was concluded that in 97.5% of patients the 370 MBq ^{131}I diagnostic scan had no additional

value over the combination of a low-dose diagnostic ^{131}I scan with 74 MBq and a serum thyroglobulin level measurement for correct clinical decision making whether the patient requires additional ^{131}I therapy.

Management of patients with negative diagnostic radioiodine scanning and elevated serum thyroglobulin levels, is a widely debated problem. It is advocated to treat patients with a negative ^{131}I diagnostic whole-body scan with an empirical therapeutic dose of 100 -300 mCi ^{131}I . However, the therapeutic benefit of this treatment is not clear. The aim of the study described in **chapter 6** was to investigate the course of serum thyroglobulin and clinical outcome in patients with differentiated thyroid carcinoma, negative diagnostic ^{131}I scanning and elevated serum thyroglobulin levels during thyroid hormone withdrawal, after treatment with the so-called "blind treatment" with high-dose ^{131}I therapy. We identified 56 patients in the above mentioned cohort of 504 patients, who were treated with a blind therapeutic dose of 150 mCi ^{131}I . Median follow-up from the blind therapeutic dose until end of observation was 4.2 years (range: 0.5 -13.5 years). Among the 56 blindly treated patients, 28 patients showed uptake at the posttherapy whole-body scan and 28 patients had a negative posttherapy whole-body scan. No differences between both groups were found in change of serum Tg before and after blind treatment. During follow-up 18 patients of the 28 patients with a positive posttherapy whole-body scan achieved remission compared to 10 of the 28 patients with a negative posttherapy whole-body scan ($P=0.06$). In the negative posttherapy whole-body scan group nine patients died because of their disease and none in the negative posttherapy group. This led to a different 5-years survival between both groups ($P=0.001$) with a better overall survival in the positive posttherapy group. It is likely that a better functional differentiation of the tumor, which is reflected by a positive posttherapy whole-body scan, is the main reason for the favorable prognosis in these patients.

Chapter 7 gives a short report of the first experience in the University Hospital Groningen of the use of ^{18}F -fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) scanning as a new diagnostic modality in differentiated thyroid cancer patients. FDG-PET was performed in 11 patients with differentiated thyroid carcinoma who all had undergone total thyroidectomy and ^{131}I ablation therapy and in whom serum thyroglobulin (median 9.7 ng/ml) during suppression therapy with thyroxine, remained detectable, despite a negative whole-body scan with 150 mCi ^{131}I . In all patients FDG-PET was read as positive. However, in seven of 11 patients (64%) other imaging techniques found no anatomical substrate and the FDG-PET was interpreted as false positive. Most of the false positive locations were considered to be cervical and thoracic lymph nodes. A change in clinical management directed by FDG-PET was made in only one patient (9%). Caution is suggested in the interpretation of abnormal uptake of FDG.

The influence of TSH stimulation on the accumulation of FDG in persistent, recurrent or metastatic differentiated thyroid carcinoma is studied in **chapter 8**. The accumulation

of ^{131}I , needed for diagnostic ^{131}I scanning, is much better during TSH stimulation. This is attained by thyroid hormone withdrawal and leads to hypothyroidism. Eight patients underwent both a FDG-PET scan during thyroid hormone suppression therapy and after thyroid hormone withdrawal. After the second FDG-PET scan, a therapeutic ^{131}I dose was administered with post-therapy scans obtained 10 days later. Findings were verified using other imaging modalities or biopsies. The FDG-PET scans during TSH suppression showed abnormalities in four patients and the FDG-PET scan during TSH stimulation in five patients. One patient showed only a positive FDG-PET scan during TSH stimulation. In two other patients the FDG-PET scan during TSH stimulation clearly identified more lesions, and in all positive patients lesion contrast was better during TSH stimulation. In two patients FDG-PET findings during TSH stimulation led to a change in clinical management. It is concluded that the performance of FDG-PET during TSH stimulation was either superior or equal to FDG-PET during TSH suppression, but never inferior.

The outcome of patients with bone metastases of differentiated thyroid carcinoma is worse compared to the overall prognosis of patients with differentiated thyroid carcinoma. In **chapter 9** the results of embolization, as a new therapeutic approach for patients with large bone metastases, are described. Five symptomatic patients, who presented with a large unresectable bone metastasis of differentiated thyroid carcinoma were treated with radioiodine and embolization. The effect of this combined treatment was compared to the effect of radioiodine without embolization in a historical control group of six patients. Serum thyroglobulin levels, pain and neurological symptoms were scored. Both groups were treated similar with total thyroidectomy followed by ablation with 5.6 GBq (= 150 mCi) ^{131}I and a second dose of 5.6 GBq ^{131}I three months later, except for embolization in the embolization group, which took place between the two radioiodine treatments. Radioiodine therapy with or without additional embolization resulted in a rapid relief of pain and neurological symptoms. However, in the embolization group serum thyroglobulin at the second ^{131}I therapy had decreased by 88.7%, which was more compared to the decrease of serum thyroglobulin in the control group (18.6%). CT-scanning showed a median volume reduction of the metastasis after radioiodine treatment combined with embolization of 52.5%. Embolization was not accompanied with severe complications and was well tolerated. This preliminary study suggests that embolization of bone metastases of differentiated thyroid carcinoma in combination with radioiodine treatment results in a better initial reduction of serum thyroglobulin level compared to radioiodine treatment alone.

In **chapter 10** a pilot study in seven patients is described in which marimastat is added to embolization in the treatment of bone metastases. Marimastat is an inhibitor of matrix metalloproteinases. These matrix metalloproteinases are required for angiogenesis. All seven patients underwent total thyroidectomy, radioiodine therapy and embolization of bone metastases. Six patients discontinued marimastat therapy after a median of 12

weeks, four because of tumor progression, two because of severe musculoskeletal symptoms. In one patient the bone metastasis showed regression after marimastat combined with embolization. It was concluded that the addition of marimastat to embolization had no clear beneficial effects. In addition, musculoskeletal adverse effects proved to be a serious drawback.